REMARKS

I. Status of the Application

Claims 48-178 are presently pending in the application. Claims 124-178 have been withdrawn from consideration by the Examiner. Claims 48-85, 87-110, 112-123 stand rejected as being obvious over Pirrung (WO/90/15070) in view of Southern (WO 89/10977) and Hayes (US 4,877,745) and Prats (US 4,937,593). Claims 76, 86, and 111 stand rejected as being obvious over Pirrung in view of Sanz and Meltzer.

Applicants believe that the current claims are patentable over the references for all the reasons previously stated in their earlier amendment. However, they are presenting the current amendments which are similar to those made in allowed parent application 09/498,554 to facilitate prosecution of the claims.

Applicants have amended the independent claims to clarify that the methods are directed to the making of an array of ligands. Support for the amendment is found at page 6 lines 24-31 where ligands are discussed. Such ligands include nucleic acids and polypeptides. The independent claims have also been amended to recite individual localized areas. Support for the amendment is found at page 25 line 25 which identifies individual reaction regions. Localized areas are alternatively referred to in the application at page 10 lines 1-5 as reaction regions. The independent claims further recite a density of localized areas on the support of at least about 1000 localized areas per cm^2 of surface of the support. Support for the amendment is found at page 25 lines 32-35. The claims have been further amended to describe the dispensing of a ligand and in some cases a nucleic acid (see claims 146 and 147 or example) in a volume of the solution in a single coupling step of less than 5 nl to occupy a localized area. Support for this amendment is found at page 25 lines 8-10 where the specification describes the step-wise dispensing of the solution in single coupling steps and at page 28 lines 11-16 where a five

nanoliter volume is dispensed. Based on the description in the specification, applicants respectfully submit that the amended claim language is fully supported by the specification.

The Examiner notes in an advisory action dated November 10, 2003 in parent application no. 09/498,554 that similar amendments overcame the rejections in that case based on Pirrung (WO/90/15070), Southern (WO 89/10977), Hayes (US 4,877,745) and Prats (US 4,937,593). Applicants respectfully submit that the presently amended claims likewise distinguish over the cited art. Accordingly, applicants respectfully request entry of the amendments and reconsideration and allowance of the claims.

Though not formally the basis for a rejection of record, Applicants wish to address each of Deeg (US 5,338,688), Khrapko (DNA Seq, Vol. 1, pp. 375-388), Brennan (US 5,474,796) and Gordon (EP 0063810) that were discussed in the advisory action dated November 10, 2003 in parent application 09/498,554 in view of the amended claims.

In the parent case, the Examiner cites Deeg for its disclosure of conventional ink jet droplet sizes of 230 picoliters and a print density of 5714 droplets per square centimeter. Applicants respectfully submit that Deeg teaches conventional ink jet printing where droplets of a certain volume are dispensed at a certain density so that they overlap to form a pattern such as a line or separate dots. The ink jet printer of Deeg is disclosed as being capable of dispensing single 230 pl droplets, as noted by the Examiner. However, applicants respectfully note that the same technology is used to provide a certain resolution when printing text, for example, so that the area of the printed image appears continuous to the viewer, i.e., certain droplet sizes are used to blend together to provide a continuous image having a certain resolution. While identifying the droplet size parameters of a standard ink-jet printing head, Deeg however discloses the

printing of only six separate reagent domains on a paper substrate for a total application of $3.9\mu l/cm^2$.

Applicants claim the dispensing in a single coupling step of less than 5 nl, whether dispensed by a piezoelectric pump, ink jet printer, ink drop printer, or other dispenser known in the art. See specification at page 18. Assuming a single dispensing at each of the six domains of Deeg, the amount dispensed at each domain is far in excess of 5 nl. In addition, Deeg teaches dispensing 1 µl volumes of sarcosine to each of the six reagent domains to produce a visible color change indicating that a reaction has taken place. Deeg provides no guidance that dispensing volumes on the order of 5 nl or less would produce the visible color change sought by Deeg to indicate that a reaction has taken place on its paper substrate. Nowhere does Deeg teach or suggest the dispensing of a volume of solution in a single coupling step of less than 5 nl (whether by a conventional ink jet printer or not) to create an array of 100 different ligands having a density of 1000 localized areas per cm^2 of the surface of the support . In addition, Deeg's conventional ink jet printer print density does not refer to the density of separate discrete features, such as ligands, on an array. It merely refers to the coverage capability of the droplets dispensed from the ink jet printer to produce a continuous image. This is evidenced by the reference to print density at Example 3 where the print density is used to create six separate reagent domains and not 192 x 192 separate domains within a square inch. Furthermore, nowhere does Deeg teach or suggest an array of 100 different ligands or a density of 1000 localized areas per square centimeter of surface of the support. Deeg teaches only a few different printing compounds in its Examples.

In the parent application, the Examiner cites Khrapko as pipetting 1 nl drops from a microcapillary fixed in a micromanipulator. At page 387 of Khrapko, a rectangular matrix of

dots is described as being prepared by microchip technology on a glass substrate having polyacrylamide gel squares. Specifically, "[a]bout 0.1 pmole of oxidized oligonucleotide was immobilized in a dot by pipetting of about 1 nl of an oligonucleotide solution with a microcapillary fixed in a micromanipulator." Khrapko, however, provides no technical disclosure of how the oligonucleotide solution is transferred from the microcapillary to the polyacrylamide gel square. Khrapko is silent as to whether fluid is forced or expelled from the microcapillary or whether conventional capillary wicking is used. Further, Khrapko provides no guidance as to whether the fluid is drawn from the capillary by contact with the polyacrylamide gel or otherwise. However, the claims require the method step of locating a dispenser to dispense a solution comprising a compound a distance away from a surface of the support and then dispensing a volume of the solution in a single coupling step of less that 5 nl from the dispenser. Khrapko does not teach, and in fact is silent on, these method steps.

In the parent case, the Examiner cites Brennen for its disclosure of 50 picoliter to 2 microliter reagent volumes. However, Brennen discloses a conventional piezoelectric pump that creates multiple droplets which are then directed to the surface of a support. The disclosed reagent volumes are then created by very hydrophobic barriers of a mask and regardless of volume dispensed (see example 2). Like Deeg, Brennen does not teach or suggest the dispensing of a volume of the solution in a single coupling step of less than 5 nl.

In the parent case, the Examiner cites Gordon for its disclosure of conventional ink jet printers to deposit 100 microliter volumes. However, Gordon (like Deeg) does not teach or suggest the dispensing of a volume of the solution in a single coupling step of less than 5 nl.

The Examiner is respectfully reminded of the reasons for allowance stated in the notice of allowance dated March 36, 2004 in parent application no. 09/498,554. Applicants respectfully request entry of the amendments and reconsideration and allowance of the amended claims.

Respectfully submitted,

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